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EWM:WP39
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PATENT APPLICATION
Docket No.: UMMC91-03A

#27
11/22/96
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appellants: Harriet L. Robinson, Ellen F. Fynan and Robert G. Webster

Serial No.: 08/009,833 Group: 1813

Filed: January 27, 1993 Examiner: L. Smith

For: IMMUNIZATION BY INOCULATION OF DNA TRANSCRIPTION UNIT

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as First Class Mail in an envelope addressed to Assistant Commissioner for Patents, Washington, D.C. 20231

on June 13, 1996 Joan Z. Graham
Date Signature

Joan Z. Graham
Typed or printed name of person signing certificate

SUPPLEMENTAL REMARKS

The Assistant Commissioner
For Patents
Washington, DC 20231

Sir:

Applicants' Attorney respectfully requests consideration of the following Supplemental Remarks, which are being submitted to present to the Patent Office information which supports the patentability of the claimed invention, and which was not publicly available until after the Amendment mailed on May 13, 1996, was submitted, and, therefore, could not have been included with the Amendment. Applicants' Attorney believes this new information, which relates to the objective considerations of *Graham v. John Deere* (383 U.S. 1, 148 USPQ 459 (1966)), will assist the

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Examiner in reconsideration of the rejection of claims under 35 U.S.C. 103.

The Court of Customs and Patent Appeals (CCPA) has indicated that evidence of objective considerations should always be evaluated. In *In re Mageli*, the CCPA stated that:

> Obviousness or unobviousness under 103 being an ultimate legal conclusion to be determined on the bases of facts established by evidence, evidence bearing on the facts is never of "no moment," is always to be considered, and accorded whatever weight it may have.

(citations omitted) (*In re Mageli*, 176 USPQ 305, 307 (CCPA 1973)). The Federal Circuit has taken a similar position to the CCPA, and has affirmed that objective considerations must always be considered by the board:

> If... a patent applicant properly presents evidence relating to these secondary considerations, the board must always consider such evidence in connection with the determination of obviousness.

(citations omitted) (*In re Sernaker*, 217 USPQ 1, 7 (Fed. Cir. 1983). The objective considerations described below and in the accompanying Declaration of William S. Rosenberg, Ph.D., arose after the date of the application. They should nevertheless be considered, as the CCPA has made it clear that facts developed after the date of the application can demonstrate nonobviousness (*In re Tiffin*, 170 USPQ 88 (CCPA 1971).

An Executed Declaration of William S. Rosenberg, Ph.D., who is the Director of Licensing & Ventures for University of Massachusetts Medical Center (one of the assignees of the current application), is being filed as Exhibit H with this paper to present further evidence of objective considerations demonstrating nonobviousness.

Remarks

In the Office action mailed from the PTO on November 13, 1995, Claims 1, 2, 4, 7-14, and 17-24 were rejected as

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being obvious over WO 90/11092 in view of Huylebroeck et al., essentially for the reasons set forth in previous Office actions.

Obviousness under 35 U.S.C. 103 is a question of law based on the factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 17, 148 USPQ 459, 467 (1966):

> Under 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the origin of the subject matter sought to be patented. As indicia of obviousness or nonobviousness, these inquiries may have relevancy (citation omitted).

The scope and content of the prior art, differences between the prior art and the claims at issue, and the level of ordinary skill in the pertinent art have been addressed at length in previous Responses. Appendix I highlights and summarizes the previous discussions of these factual inquiries.

The secondary considerations described in *Graham v. John Deere* have been accorded significant weight by the Federal Circuit, as described in *Glaros v. H.H. Robertson Co.*: "The Federal Circuit has... repeatedly emphasized the importance of the inquiry into secondary considerations, such as the commercial success of the invention and the prior failure of others, as the strongest precaution against judging an invention from the perspective of 20/20 hindsight." (224 USPQ 1037, 1038 (N.D. Ill. 1984), affirmed 230 USPQ 393 (Fed. Cir. 1986)). Further, in *Stratoflex, Inc. v. Aeroquip Corp.*, the Federal Circuit stated:

> It is jurisprudentially inappropriate to disregard any relevant evidence on any issue in any case, patent cases included. Thus evidence rising out of the so-called "secondary

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> considerations" must always when present be considered en route to a determination of obviousness.... Indeed, evidence of secondary considerations may often be the most probative and cogent evidence in the record. It may often establish that an invention appearing to have been obvious in light of the prior art was not. It is to be considered as part of all the evidence, not just when the decisionmaker remains in doubt after reviewing the art.

(218 USPQ 871, 879 (Fed. Cir. 1983)).

Secondary considerations set forth in *Graham v. John Deere* include, but are not limited to, commercial success, long felt but unsolved needs, and failure of others. As shown by the following, the claimed invention has met a long-standing need for improved vaccines, was not expected by those in the field to work, yielded surprising results, and has met with clear commercial success, as evidenced by the fact that it is the subject of one of the 10 largest licensing agreements for an American University. It is noteworthy that the subject invention has had such commercial success, even though a patent has not yet issued. The commercial success is due to the nature of the claimed invention, and not to any other economic or commercial factors unrelated to the subject matter of the patent application.

Information clearly showing the commercial success of the invention has recently become available. In May, 1996, a 42 million dollar, licensing agreement was reached between University of Massachusetts Medical Center (UMMC) and Pasteur Merieux-Connaught (Pasteur), for exclusive rights to the methods of vaccination of humans encompassed by the claims of the invention. This licensing agreement (the Pasteur agreement) has been described in a national publication which monitors current events in biotechnology as "among the 10 largest biotechnology deals signed by a U.S. university" (BioWorld Today, May 16, 1996, attached as Exhibit A). Nationwide coverage of the agreement occurred:

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the agreement was described by the Boston Globe (Exhibit B); the Telegraph (Nashua, New Hampshire) (Exhibit C); the Worcester Telegram & Gazette (Exhibit D); the Boston Herald (Exhibit E); Reuters (Exhibit F); the American Political Network (Exhibit G); and the Associated Press, as well as several television news programs and National Public Radio. Pasteur Merieux-Connaught is one of the world's largest vaccine manufacturers (American Political Network, Exhibit G). Furthermore, as described in the accompanying Declaration (Exhibit H) of Dr. William S. Rosenberg, Director of Licensing & Ventures for UMMC, other large pharmaceutical companies have also expressed interest in the technology. A company in addition to Pasteur also made an offer of terms for a licensing agreement, and companies other than Pasteur are interested in licensing additional uses of the claimed invention, both in humans and in animals.

The Pasteur agreement pertains to use of DNA vaccination technology for humans and, in particular, relates to development of vaccines to protect humans against thirteen different diseases, including influenza, by injection of purified genetic material from the infectious agent. This licensed subject matter is the same as that disclosed and claimed in the current application. Furthermore, as is also stated in the accompanying Declaration of Dr. William Rosenberg (Exhibit H), other companies have expressed interest in licensing further subject matter that is not covered by the Pasteur agreement, including veterinary applications of the technology, as well as use of the technology for treating human diseases not included in the Pasteur agreement. The Pasteur agreement, as well as the continued interest by other companies, clearly demonstrates that the current invention has had, and continues to have, significant commercial success. The commercial success of the current

invention is due to the nature of the claimed invention, and not to other technical developments or commercial considerations in the field of vaccine technology.

Other secondary considerations also demonstrate the nonobviousness of the claimed invention. There has been a long felt but unfulfilled need in the area of vaccine technology for improved vaccines that have high immunogenicity, are inexpensive to produce, are easily transported and stored, and minimize the risk of inadvertent infection. The drawbacks to current vaccines include low immunogenicity, particularly for peptide-based vaccines and also for killed-organism vaccines in which conformational epitopes may be distorted; expensive production, transportation and storage, particularly due to the need for refrigeration; and risk of inadvertent infection from live vaccines, as described in the IAC Newsletter Database, TB Weekly for November 13, 1995 (Exhibit I).

Vaccination using DNA, which is the subject of the claims rejected in the current application, addresses the deficiencies of presently used peptide- or killed-organism-based vaccines, and provides additional advantages. As further described in the IAC Newsletter (Exhibit I), DNA vaccines are inexpensive to produce, are stable without refrigeration, and do not cause inadvertent infection. Furthermore, DNA vaccines may provide improved vaccine efficacy, lower required dosages of foreign antigens, reduced side effects, and increase ability for combination vaccines. These advantages are important for developed as well as developing regions of the world, with stability being particularly important for the developing regions of the world, where refrigeration of presently available vaccines is difficult or prohibitively expensive. Thus, the claimed methods of immunizing against disease have addressed the long-felt needs of vaccine technology.

The significance of DNA vaccination is further emphasized in Exhibit J (Newsday), published October 3, 1995. There, the writer scoffed at the idea of vaccinating with DNA and stated that one of ordinary skill in the art *would not have expected* vaccination using DNA transcription units to be successful. As stated in Exhibit J,

> It wasn't long ago that nobody would have bet a buck on the idea of shooting individual genes - what scientists refer to as 'naked DNA' - directly into people to protect against infection. Some disease specialists, in fact, bluntly called the idea of injecting DNA into a patient without a protein coat or a virus shell outrageous, or, worse, dangerous. In the last six months, however, researchers have begun doing just that, prompted by successful animal studies that now have scientists using words like 'surprising' and 'revolutionary.'

This report was published over *three and a half years* after Applicants had demonstrated protection using DNA vaccination. This evidence of initial disbelief of those in the field of the invention is highly indicative of the nonobviousness of the invention. The Federal Circuit has stated that "expressions of disbelief by experts constitute strong evidence of nonobviousness" (*Environmental Designs, Ltd. v. Union Oil Co. of Calif.*, 218 USPQ 865 (Fed.Cir. 1983)). The disbelief of researchers is a clear indication that the current invention was a surprising discovery.

The unexpected success of vaccination with DNA is further emphasized by the fact that, even several years after Applicants' application was filed, the technology is still considered to be groundbreaking news in vaccine development. For example, Cable News Network (CNN) characterized the DNA vaccination technology as "a potentially powerful type of vaccine, unlike anything now available" (Transcript of HealthWorks show, CNN, June 18, 1994) (Exhibit K). Even today, the DNA vaccine technology is considered by those in the field to be a significant

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advancement in the art. As described in the Harvard Health Letter, for March, 1996 (Exhibit L), DNA vaccination to protect against disease is one of "ten new discoveries that [faculty advisors] predict will have a significant and far-reaching impact on human health." Thus, despite initial disbelief, the importance of DNA vaccines has become evident, and has been given professional recognition as a critical technology for vaccine development.

Conclusion

In view of the discussion of the factual inquiries of *Graham v. John Deere Co.*, and particularly in view of the evidence of objective considerations, including the commercial success of the invention, as well as the arguments previously made, Applicants' attorney requests that the Examiner reconsider and withdraw the rejection of the claims under 35 U.S.C. 103.

If the Examiner believes that a telephone conversation will expedite prosecution of this application, the Examiner is encouraged to call Applicants' Attorney at (617) 861-6240.

Respectfully submitted,

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APPENDIX I Summary of First Three Factors in *Graham v. John Deere* Analysis

Factor 1: Scope and Content of Prior Art

WO 90/11092 (Felgner et al., assigned to Vical, Inc.) describes methods of delivering RNA or DNA polynucleotides into a vertebrate cell by delivery into the interstitial space (i.e., into the intercellular, fluid matrix among the fibers of organ tissues or fibers in the walls of vessels or chambers, or within connective tissue or bone, as described at page 23, lines 8-23), for vaccination or gene therapy. WO 90/11092 states that various routes of administration and pharmaceutically acceptable vehicles can be used, and focuses on use of the methods for transient gene therapy to treat genetically-based diseases such as muscular dystrophy, cystic fibrosis, genetic defects of intermediary metabolism, Alzheimer's disease, liver and lung disease caused by alpha-1-antitrypsin deficiency, and cancers. WO 90/11092 also states that transient gene therapy can be used to increase the resistance of an AIDS patient to HIV infection.

In its exemplification, WO 90/11092 describes mRNA vaccination of mice to produce gp120 protein of the human immunodeficiency virus (HIV), and eliciting of an antibody response. WO 90/11092 does not teach or describe generation of a cytotoxic T cell response. WO 90/11092 does not teach or describe actual use of any antigen other than HIV gp-120 to generate an immune response. WO 90/11092 does not describe any protective immune response.

Huylebroeck et al. (*Tech. Adv. in Vaccine Dev. 84*:279-293 (1988)) describe expression of a membrane-bound and a secreted form of influenza virus HA protein in a transient expression system based on SV40 plasmid vectors, and indicate that "Influenza virus HA is considered to be the

most important viral antigen connected with the frequent antigenic changes of the virus" (p. 280).

Factors 2 and 3: differences between the prior art and the claims at issue and level of ordinary skill in the art

The claims at issue describe immunization of a vertebrate by a DNA transcription unit, and protection of the vertebrate against disease.

The cited prior art does not teach or describe protection against disease; furthermore, one of ordinary skill in the art, given the prior art, would not have had a reasonable expectation that protection against disease could have been achieved.

As discussed in the Amendment filed May 13, 1996, no teaching or suggestion supporting the combination of the references is found in the prior art of record. WO 90/11092 does not teach or suggest that one of ordinary skill should look to a reference concerning influenza: WO 90/11092 does not mention influenza at all. Huylebroeck et al., which describes the importance of the *protein*, does not teach or suggest that one of ordinary skill should look to a reference pertaining to use of *polynucleotides* for gene therapy or vaccination. Huylebroeck et al. teaches a protein that is considered to be the most important viral antigen connected with frequent antigenic changes of the virus; one of ordinary skill in the art would have been motivated to use the protein, and not a polynucleotide. Thus, one of ordinary skill in the art would not have been motivated to combine the teachings of WO 90/11092 with those of Huylebroeck et al.

Furthermore, even if the teachings of WO 90/11092 are combined with those of Huylebroeck et al., the current invention would not have been obvious, as there is no reasonable likelihood of success in achieving a protective response to immunization with the current methods, viewed

in the light of the prior art. WO 90/11092 describes introduction into a mouse of a construct that encodes a protein which is pathogenic to humans but not to mice; therefore, the teachings of WO 90/11092 cannot show protection. Furthermore, WO 90/11092 showed only an antibody response to the gp120 protein. It is known in the art that the presence of antibody to HIV proteins in no way indicates protective immunity (see p. 477 of Kuby, J., Immunology, submitted as Exhibit M). Therefore, one of ordinary skill in the art would not have had a reasonable expectation of success in protecting against disease upon challenge.

In addition, the teaching at the time of the invention was that microgram (10^{-6} gram) quantities of protein would have been necessary to provide protective immunization (see Fields, Virology, Vol. I, Orthomxyoviruses, pp. 1126-1127, concerning the amounts of protein used in inactivated influenza virus vaccines to obtain protection; a copy of this reference was attached as Exhibit B to the Amendment filed on February 22, 1994). However, only picogram (10^{-12} gram) levels of protein expression resulted from the method used in WO 90/11092 (see Figure 3 of WO 90/11092). That is, the quantity of protein produced in WO 90/11092 was 10^{6}-fold less than the quantities the art said would have been necessary to provide protection. One of ordinary skill in the art would not have had a reasonable expectation that such minute levels of protein expression could have achieved protective immunization. Despite this teaching, Applicants used DNA vaccination and provided a protective effect.

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